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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re the application of:
KUSTERS ET AL.

Serial Number: 09/904,994

Group Art Unit: To be assigned

Filed: July 13, 2001

Examiner: To be assigned

For: HELICOBACTER FELIS VACCINE

CLAIM TO PRIORITY UNDER 35 USC 119

Assistant Commissioner of Patents
Washington, D.C. 20231

July 30, 2001

Sir:

The benefit of the filing date of the following prior foreign application is hereby requested for the above-identified application, and the priority provided in 35 USC 119 is hereby claimed:

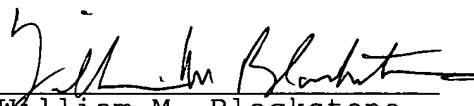
European Patent Application No. 00202565.8, filed July 17, 2000

In support of this claim, the requisite certified copy of said original foreign application is filed herewith along with a verified English translation thereof.

It is requested that the file of this application be marked to indicate that the Applicant has complied with the requirements of 35 USC 119 and that the Patent and Trademark Office kindly acknowledge receipt of this document.

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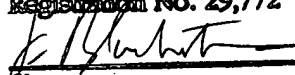
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Sheet 2 of the certificate
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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Helicobacter felis vaccine.

5 The present invention relates to novel *Helicobacter* urease subunit polypeptides, nucleic acid sequences encoding these polypeptides, to the polypeptides for use in vaccines and for use in the manufacturing thereof, to vaccines comprising said polypeptides and to methods for the preparation of such vaccines. Further, the invention relates to diagnostic methods for the detection of the nucleic acid sequences, the polypeptides and antibodies against the polypeptides.

10 Several *Helicobacter* species are the cause of pathogenesis of the gastric epithelium. *Helicobacter pylori*, and to a lesser extent *H. heilmannii* are known to cause gastritis, a major factor in the development of peptic ulcers and gastric lymphoma in humans. *Helicobacter felis* is most likely the cause of gastric infections in both cats and dogs. In order to survive the highly acidic environment of the stomach, members of the
15 *Helicobacter* family produce an urease that is capable of hydrolysing the urea present in gastric juice. This hydrolysis sets free an amount of NH_4OH that suffices to neutralise the environment of the bacterium. It is known, that the urease plays a role in the colonisation of the bacterium as well as in its pathogenesis.

20 Genes encoding urease have been described and sequenced for both *Helicobacter pylori* (Labigne et al., J. Bacteriol. 173: 1920-1931 (1991)) and *Helicobacter felis* (Ferrero et al., Molec. Microbiol. 9, 323-333 (1993)). Of the seven genes involved in urease expression and secretion, only two genes encode the two structural subunits urease A and B of the urease enzyme; ureA and ureB. These two polypeptides form a polypeptide complex having urease activity.

25 Vaccines against infections caused by both *H. pylori* and *felis* have been made and have been the subject of i.a. International Patent Applications WO 94/09823 and WO 96/34624. Several attempts have been made, to use *H. pylori* urease as a vaccine component for the protection of cats against *H. felis* infection. Although indeed a certain level of protection can be obtained, the results are far from the 100 % protection that
30 would be desirable. From animal experiments published so far it becomes clear that a significant number of animals vaccinated with *H. pylori* is not at all protected against subsequent challenge with *H. felis*. Protection of cats vaccinated with purified urease from either *H. felis* or *pylori* has not been described. Vaccinating cats with *H. felis* whole cell lysates might theoretically be feasible but is not a practical option. This is because in
35 spite of many attempts for improvement, *H. felis* is difficult to grow. There clearly is a need for an efficacious vaccine, based upon homologous components, and it is clear that the known *H. felis* urease does not confer full protection.

40 It is i.a. an object of the present invention to provide a *H. felis* urease which is able to induce protection against *Helicobacter felis* infection in dogs and cats. It was surprisingly found now, that in *H. felis* a second urease exists, of which the genes encoding the structural subunits share only low homology with the known *H. felis* ureA and B genes. The novel urease is named ureaseXY, in order to discriminate it from the known urease AB. The newly found urease has been discovered in *H. felis*, and is not present in *H.*
45 *pylori*.

The overall genetic structure of the genes encoding the two structural urease subunits, UreX and UreY is comparable to that of the known UreA and B in *H. felis* and *H. pylori*. The sequence homology is however surprisingly low. It was even more surprisingly found, that the homology between the ureA and B genes and the novel ureX and Y
50 genes in one single *H. felis* strain is even strikingly lower than the homology between the various ureA and B genes from the various *Helicobacter* species.

Table 1a, 1b and 1c show the comparison of the ureX and Y gene and the polypeptides they encode from five different *Helicobacter felis* species, with the ureA and B genes and polypeptides from *Helicobacter felis*, *pylori* and *heilmannii*.

The level of homology of the genes encoding the novel structural urease subunits X and Y and the polypeptides they encode as compared to that of known ureA and B genes and polypeptide subunits is presented in table 1a, b and c.

Reference molecule : <i>H. felis</i> ureX CS1	a.a.	n.a.
<i>H. felis</i> ureA	50 %	57 %
<i>H. pylori</i> ureA	52 %	60 %
<i>H. heilmannii</i> ureA	54 %	62 %
<i>H. felis</i> strain Kukka ureX	100 %	91 %
<i>H. felis</i> strain Ds4 ureX	99 %	91 %
<i>H. felis</i> strain 2301 ureX	99 %	91 %
<i>H. felis</i> strain 390 ureX	99 %	91 %

Table 1a: amino acid and nucleic acid homology between the *H. felis* ureX and various ureA subunits.

Reference molecule : <i>H. felis</i> ureY CS1	a.a.	n.a.
<i>H. felis</i> ureB	73 %	71 %
<i>H. pylori</i> ureB	73 %	70 %
<i>H. heilmannii</i> ureB	74 %	71 %
<i>H. felis</i> strain Kukka ureY	99 %	95 %
<i>H. felis</i> strain Ds4 ureY	98 %	94 %
<i>H. felis</i> strain 2301 ureY	99 %	95 %

Table 1b: amino acid and nucleic acid homology between the *H. felis* ureY and various ureB subunits.

Reference molecule: <i>H. felis</i> ureXY CSI	n.a.
<i>H. felis</i> ureAB	67 %
<i>H. pylori</i> ureAB	67 %
<i>H. heilmannii</i> ureAB	68 %
<i>H. felis</i> strain Kukka ureXY	94 %
<i>H. felis</i> strain Ds4 ureXY	94 %
<i>H. felis</i> strain 2301 ureXY	94 %

Table 1c: nucleic acid homology between *H. felis* ureXY and various ureAB genes.

One embodiment of the invention thus relates to nucleic acid sequences encoding the novel urease X and Y subunits.

5 First of all, this embodiment of the invention relates to nucleic acid sequences encoding two subunits of a urease complex such as expressed by *Helicobacter felis*, that have at least 85 % homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of one of the subunits. Still even longer fragments, with a length of at least 55, 60 or 70 nucleic acids are in that order even more preferred.

10 A preferred form of this embodiment relates to nucleic acid sequences that encode the urease X subunit polypeptide or the urease Y subunit polypeptide and that have at least 85 % homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of the urease X subunit polypeptide or the urease Y subunit polypeptide. Merely as an example: the nucleic acid sequence encoding the urease X subunit of *Helicobacter felis* strain CS1 starts at position 206/207/208 (GTG) (See figure 1a (1)) and stops at position 884/885/886 (TAA). the nucleic acid sequence encoding the urease Y subunit of *Helicobacter felis* strain CS1 starts at position 897/898/899 (ATG) and stops at position 2601/2602/2603 (TAG). Still even longer fragments, with a length of at least 55, 60 or 70 nucleic acids are in that order even more preferred.

25 A more preferred form of this embodiment relates to nucleic acid sequences having at least 90 %, preferably 94 %, more preferably 97 % homology therewith.

30 The determination of the homology percentages was done with the computer program Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA. Settings used for the nucleic acid comparisons are indicated in figures 1a, 1b and 1c.

35 Since the present invention discloses nucleic acid sequences encoding novel structural *Helicobacter felis* urease subunits, it is now for the first time possible to obtain such polypeptides in sufficient quantities. This can e.g. be done by using expression systems to express the genes encoding the UreX and UreY subunits. Therefore, in a more preferred embodiment, the invention relates to DNA fragments comprising a nucleic acid sequence according to the invention. Such DNA fragments can e.g. be plasmids, into which a nucleic acid sequence according to the invention is cloned. Such DNA fragments are useful e.g. for enhancing the amount of DNA for use as a probe, as described below.

40 An essential requirement for the expression of the nucleic acid sequence is an adequate promoter operably linked to the nucleic acid sequence. It is obvious to those skilled in the art that the choice of a promoter extends to any eukaryotic, prokaryotic or viral promoter capable of directing gene transcription in cells used as host cells for protein expression.

45 Therefore, an even more preferred form of this embodiment relates to a recombinant DNA molecule comprising a DNA fragment or a nucleic acid sequence according to the invention that is placed under the control of a functionally linked promoter. This can be obtained by means of e.g. standard molecular biology techniques. (Maniatis/Sambrook (Sambrook, J. Molecular cloning: a laboratory manual, 1989. ISBN 0-87969-309-6).

Functionally linked promoters are promoters that are capable of controlling the transcription of the nucleic acid sequences to which they are linked.

When the host cells are bacteria, useful expression control sequences which may be used include the Trp promoter and operator (Goeddel, et al., Nucl. Acids Res., 8, 4057, 1980); the lac promoter and operator (Chang, et al., Nature, 275, 615, 1978); the outer membrane protein promoter (Nakamura, K. and Inouge, M., EMBO J., 1, 771-775, 1982); the bacteriophage lambda promoters and operators (Remaut, E. et al., Nucl. Acids Res., 11, 4677-4688, 1983); the α -amylase (*B. subtilis*) promoter and operator, termination sequences and other expression enhancement and control sequences compatible with the selected host cell.

When the host cell is yeast, useful expression control sequences include, e.g., α -mating factor. For insect cells the polyhedrin or p10 promoters of baculoviruses can be used (Smith, G.E. et al., Mol. Cell. Biol. 3, 2156-65, 1983). When the host cell is of mammalian origin illustrative useful expression control sequences include the SV-40 promoter (Berman, P.W. et al., Science, 222, 524-527, 1983) or the metallothionein promoter (Brinster, R.L., Nature, 296, 39-42, 1982) or a heat shock promoter (Voellmy et al., Proc. Natl. Acad. Sci. USA, 82, 4949-53, 1985).

Bacterial, yeast, fungal, insect and mammalian cell expression systems are very frequently used systems. Such systems are well-known in the art and generally available, e.g. commercially through Clontech Laboratories, Inc. 4030 Fabian Way, Palo Alto, California 94303-4607, USA. Next to these expression systems, parasite-based expression systems are very attractive expression systems. Such systems are e.g. described in the French Patent Application with Publication number 2 714 074, and in US NTIS Publication No US 08/043109 (Hoffman, S. and Rogers, W.: Public. Date 1 December 1993).

Thus a still even more preferred form of this embodiment of the invention relates to Live Recombinant Carrier micro-organisms (LRCs) comprising a gene encoding the UreX or UreY polypeptide or an immunogenic fragment thereof according to the invention. Such micro-organisms are e.g. bacteria and viruses. These LRC micro-organisms are micro-organisms in which additional genetic information, in this case a gene encoding the UreX or UreY polypeptide or an immunogenic fragment thereof according to the invention has been cloned. Animals infected with such LRCs will produce an immunogenic response not only against the immunogens of the vector, but also against the immunogenic parts of the polypeptide(s) for which the genetic code is additionally cloned into the LRC, e.g. the ureX or Y gene.

As an example of bacterial LRCs, attenuated Salmonella strains known in the art can attractively be used.

Live recombinant carrier parasites have i.a. been described by Vermeulen, A. N. (Int. Journ. Parasitol. 28: 1121-1130 (1998))

Also, LRC viruses may be used as a way of transporting the nucleic acid sequence into a target cell. Live recombinant carrier viruses are also called vector viruses. The site of integration of the gene encoding a UreX or Y polypeptide may be a site in a viral gene that is not essential to the virus, or a site in an intergenic region. Viruses often used as vectors are Vaccinia viruses (Panicali et al; Proc. Natl. Acad. Sci. USA, 79: 4927 (1982), Herpesviruses (E.P.A. 0473210A2), and Retroviruses (Valerio, D. et al; in Baum, S.J., Dicke, K.A., Lotzova, E. and Pluznik, D.H. (Eds.), Experimental Haematology today - 1988. Springer Verlag, New York: pp. 92-99 (1989)).

Figure 1a (3)

Figure 1a (4)

The technique of *in vivo* homologous recombination, well-known in the art, can be used to introduce a recombinant nucleic acid sequence into the genome of a bacterium, parasite or virus of choice, capable of inducing expression of the inserted nucleic acid sequence according to the invention in the host animal.

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Finally another form of this embodiment of the invention relates to a host cell comprising a nucleic acid sequence encoding a polypeptide according to the invention, a DNA fragment comprising such a nucleic acid sequence or a recombinant DNA molecule comprising such a nucleic acid sequence under the control of a functionally linked

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promotor. This form also relates to a host cell containing a live recombinant carrier containing a nucleic acid molecule encoding a UreX or Y polypeptide or an immunogenic fragment thereof according to the invention. A host cell may be a cell of bacterial origin, e.g. *Escherichia coli*, *Bacillus subtilis* and *Lactobacillus* species, in combination with bacteria-based plasmids as pBR322, or

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bacterial expression vectors as pGEX, or with bacteriophages. The host cell may also be of eukaryotic origin, e.g. yeast-cells in combination with yeast-specific vector molecules, or higher eukaryotic cells like insect cells (Luckow et al; Bio-technology 6: 47-55 (1988)) in combination with vectors or recombinant baculoviruses, plant cells in combination with e.g. Ti-plasmid based vectors or plant viral vectors (Barton, K.A. et al; Cell 32: 1033

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(1983), mammalian cells like Hela cells, Chinese Hamster Ovary cells (CHO) or Crandell Feline Kidney-cells, also with appropriate vectors or recombinant viruses.

25

Another embodiment of the invention relates to the polypeptides encoded by the nucleic acid sequences, i.e. the urease X subunit and the urease Y subunit and to immunogenic fragments thereof according to the invention.

30

Therefore, this embodiment of the invention relates to the *Helicobacter felis* urease X polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or an immunogenic fragment of that polypeptide with a

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length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY. Preferably, the length is more than 40 amino acids, preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference.

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This embodiment of the invention also relates to the *Helicobacter felis* urease Y polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or an immunogenic fragment of that polypeptide with a

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length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY. Preferably, the length is more than 40 amino acids, preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference.

50

As for the nucleotide sequence comparison, the comparison between the various amino acid sequences was made using Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA. Settings used for the amino acid comparisons are indicated in figures 1a, 1b and 1c.

5 It will be understood that, for the particular polypeptides embraced herein, natural variations can exist between individual *Helicobacter felis* strains. These variations may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions, substitutions, insertions, inversions or additions of (an) amino acid(s) in said
10 sequence. Amino acid substitutions which do not essentially alter biological and immunological activities, have been described, e.g. by Neurath et al in "The Proteins" Academic Press New York (1979). Amino acid replacements between related amino acids or replacements which have occurred frequently in evolution are, inter alia, Ser/Ala, Ser/Gly, Asp/Gly, Asp/Asn, Ile/Val (see Dayhof, M.D., Atlas of protein sequence and structure, Nat. Biomed. Res. Found., Washington D.C., 1978, vol. 5, suppl. 3). Other
15 amino acid substitutions include Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Thr/Phe, Ala/Pro, Lys/Arg, Leu/Ile, Leu/Val and Ala/Glu. Based on this information, Lipman and Pearson developed a method for rapid and sensitive protein comparison (Science, 227, 1435-1441, 1985) and determining the functional similarity between
20 homologous proteins. Such amino acid substitutions of the exemplary embodiments of this invention, as well as variations having deletions and/or insertions are within the scope of the invention as long as the resulting polypeptides retain their immunoreactivity. Thus, variations not essentially influencing the immunogenicity of the polypeptide compared to the wild type polypeptide as depicted in SEQ ID NO: 2 or 3 are considered
25 to fall within the scope of the invention. Those variations in the amino acid sequence of a certain structural subunit X or Y according to the invention that still provide a polypeptide capable of inducing an immune response against infection with *H. felis* or at least against the clinical manifestations of the infection are considered as "not essentially influencing the immunogenicity".

30 When a polypeptide is used for e.g. vaccination purposes or for raising antibodies, it is however not necessary to use the whole polypeptide. It is also possible to use a fragment of that polypeptide that is capable, as such or coupled to a carrier such as e.g. KLH, of inducing an immune response against that polypeptide, a so-called
35 immunogenic fragment. An "immunogenic fragment" is understood to be a fragment of the full-length polypeptide of the structural subunit X or Y, that still has retained its capability to induce an immune response in the host, i.e. comprises a B- or T-cell epitope. At this moment, a variety of techniques is available to easily identify DNA fragments encoding antigenic fragments (determinants). The method described by
40 Geysen et al (Patent Application WO 84/03564, Patent Application WO 86/06487, US Patent NR. 4,833,092, Proc. Natl Acad. Sci. 81: 3998-4002 (1984), J. Imm. Meth. 102, 259-274 (1987), the so-called PEPSCAN method is an easy to perform, quick and well-established method for the detection of epitopes; the immunologically important regions of the polypeptide. The method is used world-wide and as such well-known to man
45 skilled in the art. This (empirical) method is especially suitable for the detection of B-cell epitopes. Also, given the sequence of the gene encoding any protein, computer algorithms are able to designate specific polypeptide fragments as the immunologically important epitopes on the basis of their sequential and/or structural agreement with epitopes that are now known. The determination of these regions is based on a
50 combination of the hydrophilicity criteria according to Hopp and Woods (Proc. Natl. Acad. Sci. 78: 38248-3828 (1981)), and the secondary structure aspects according to

Figure 1b

5 Chou and Fasman (Advances in Enzymology 47: 45-148 (1987) and US Patent 4,554,101). T-cell epitopes can likewise be predicted from the sequence by computer with the aid of Berzofsky's amphiphilicity criterion (Science 235, 1059-1062 (1987) and US Patent application NTIS US 07/005,885). A condensed overview is found in: Shan Lu
on common principles: Tibtech 9: 238-242 (1991), Good et al on Malaria epitopes;
Science 235: 1059-1062 (1987), Lu for a review; Vaccine 10: 3-7 (1992), Berzowsky for
HIV-epitopes; The FASEB Journal 5:2412-2418 (1991).

10 Vaccines against e.g. *Helicobacter pylori*, which has only one urease, can be made on the basis of this urease, as was described above. In the specific case of *Helicobacter felis* however a vaccine based upon the known *Helicobacter felis* structural subunits ureA and B is not capable of providing sufficient protection against *Helicobacter felis* infection: immunity against structural subunits ureA and B allegedly does not neutralise the urease activity of the newly found heterologous structural subunits UreX and Y.

15 Therefore, vaccines for the protection of animals against *Helicobacter felis* infection should at least be directed against the novel urease XY.

20 Therefore, one form of still another embodiment of the invention relates to vaccines capable of protecting mammals such as dogs and cats against *Helicobacter felis* infection, that comprise the structural subunit X or Y, preferably X and Y, more preferably X, Y, A and B, or an immunogenic fragment of X and/or Y according to the invention together with a pharmaceutically acceptable carrier.

25 Still another embodiment of the present invention relates to the polypeptides according to the invention for use in a vaccine.

In still another embodiment, the polypeptide according to the invention is for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

30 One way of making a vaccine according to the invention is by biochemical purification of the ureaseXY polypeptide or its subunits from a bacterial culture. This can e.g. be done by centrifugation of the bacteria, and the use of gel-filtration columns for separation of the urease polypeptide or its subunits from other components. Further purification may e.g. be done by selective precipitation in ammonium-sulphate, followed by centrifugation,
35 gel electrophoresis and, if desired, separation from the urease AB subunits and dissolving the pellet in a suitable buffer. This is however a time-consuming way of making the vaccine, especially where *Helicobacter felis* is difficult to grow.

40 It is therefore much more convenient to use the expression products of the genes encoding the urease X and Y subunits according to the invention in vaccines. Such vaccines can easily be made by admixing ureaseXY or an UreX or Y subunit or an immunological fragment thereof according to the invention with a pharmaceutically acceptable carrier as described below.

45 Furthermore vaccines can comprise live recombinant carriers as described above, capable of expressing ureaseXY, an UreX or UreY subunit or immunogenic fragments thereof according to the invention. Such vaccines, e.g. based upon a *Salmonella* carrier or a viral carrier infecting the gastric epithelium have the advantage over subunit vaccines that they better mimic the natural way of infection of *Helicobacter felis*.

50 Moreover, their self-propagation is an advantage since only low amounts of the recombinant carrier are necessary for immunisation.

Vaccines described above all contribute to active vaccination, i.e. the host's immune system is triggered by the UreX and/or Y polypeptide or immunogenic fragments thereof, to make antibodies against these polypeptides.

- 5 Alternatively, such antibodies can be raised in e.g. rabbits or can be obtained from antibody-producing cell lines as described below. Such antibodies can then be administered to the host animal. This method of vaccination, passive vaccination, is the vaccination of choice when an animal is already infected, and there is no time to allow the natural immune response to be triggered. It is also the preferred method for
- 10 vaccinating immune-compromised animals. Administered antibodies against *Helicobacter* UreX or UreY can in these cases bind directly to the urease excreted by the bacteria. This has the advantage that the urease activity is directly eliminated, thus resulting in acidification of the environment and decreased or stopped *Helicobacter* growth.
- 15 Therefore, one other form of this embodiment of the invention relates to vaccines comprising antibodies against *Helicobacter felis* urease X polypeptides that have an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or immunogenic fragments of that polypeptide with a length of at least 40 amino acids that are capable of inducing an immune response against ureaseXY or antibodies against
- 20 *Helicobacter felis* urease Y polypeptides that have an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or immunogenic fragments of that polypeptide with a length of at least 40 amino acids that are capable of inducing an immune response against ureaseXY.
- 25 Vaccines can also be based upon host cells as described above, that comprise ureaseXY, an UreX or UreY subunit or immunogenic fragments thereof according to the invention.

- 30 An alternative and efficient way of vaccination is direct vaccination with DNA encoding the relevant antigen. Direct vaccination with DNA encoding polypeptides has been successful for many different polypeptides. (As reviewed in e.g. Donnelly et al., The Immunologist 2: 20-26 (1993)). This way of vaccination is very attractive for the vaccination of both cats and dogs against *Helicobacter felis* infection.
- 35 Therefore, still other forms of this embodiment of the invention relate to vaccines comprising nucleic acid sequences encoding a polypeptide according to the invention or immunogenic fragments thereof according to the invention, and to vaccines comprising DNA fragments that comprise such nucleic acid sequences.
- 40 Still other forms of this embodiment relate to vaccines comprising recombinant DNA molecules according to the invention.
- DNA vaccines can easily be administered through intradermal application e.g. using a needle-less injector. This way of administration delivers the DNA directly into the cells of the animal to be vaccinated. Amount of DNA in the microgram range between 1 and 100 µg provide very good results.

- 45 In a further embodiment, the vaccine according to the present invention also comprises antigens from other dog or cat pathogenic organisms and viruses, or genetic information encoding such antigens. Such organisms and viruses are e.g. Feline Infectious Peritonitis virus, Feline Immune deficiency virus, Canine and Feline Parvovirus,
- 50 Distemper virus, Adenovirus, Calicivirus, *Bordetella bronchiseptica*, *Borrelia burgdorferi*, *Leptospira interrogans*, *Chlamydia* and *Bartonella henselae*.

Also, the present invention relates to polypeptides according to the invention for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

- 5 All vaccines according to the present invention comprise a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier can be e.g. sterile water or a sterile physiological salt solution. In a more complex form the carrier can e.g. be a buffer.

- 10 Vaccines according to the present invention may in a preferred presentation also contain an adjuvant. Adjuvants in general comprise substances that boost the immune response of the host in a non-specific manner. A number of different adjuvants are known in the art. Examples of adjuvants are Freund's Complete and Incomplete adjuvant, vitamin E, non-ionic block polymers, muramyl dipeptides, Quil A^(R), mineral oil e.g. Bayol^(R) or Markol^(R), vegetable oil, and Carbopol^(R) (a homopolymer), or Diluvac^(R) Forte.

- 15 The vaccine may also comprise a so-called "vehicle". A vehicle is a compound to which the polypeptide adheres, without being covalently bound to it. Often used vehicle compounds are e.g. aluminium hydroxide, -phosphate or -oxide, silica, Kaolin, and Bentonite.

- 20 A special form of such a vehicle, in which the antigen is partially embedded in the vehicle, is the so-called ISCOM (EP 109.942, EP 180.564, EP 242.380)

In addition, the vaccine may comprise one or more suitable surface-active compounds or emulsifiers, e.g. Span or Tween.

- 25 Often, the vaccine is mixed with stabilisers, e.g. to protect degradation-prone polypeptides from being degraded, to enhance the shelf-life of the vaccine, or to improve freeze-drying efficiency. Useful stabilisers are i.a. SPGA (Bovarnik et al; J. Bacteriology 59: 509 (1950)), carbohydrates e.g. sorbitol, mannitol, trehalose, starch, sucrose, dextran or glucose, proteins such as albumin or casein or degradation products thereof, and buffers, such as alkali metal phosphates.

- 30 In addition, the vaccine may be suspended in a physiologically acceptable diluent. It goes without saying, that other ways of adjuvating, adding vehicle compounds or diluents, emulsifying or stabilising a polypeptide are also embodied in the present invention.

- 35 Vaccines according to the invention that comprise the UreX or UreY subunit polypeptide can very suitably be administered in amounts ranging between 1 and 100 micrograms, although smaller doses can in principle be used. A dose exceeding 100 micrograms will, although immunologically very suitable, be less attractive for commercial reasons.

- 40 Vaccines based upon live attenuated recombinant carriers, such as the LRC-viruses and bacteria described above can be administered in much lower doses, because they multiply themselves during the infection. Therefore, very suitable amounts would range between 10^3 and 10^9 CFU/PFU for respectively bacteria and viruses.

- 45 Many ways of administration can be applied. Intranasal application is a frequently used way of administering a vaccine. Oral application is also an attractive way of administration, because the infection is often located in the upper digestive tract. A preferred way of oral administration is the packaging of the vaccine in capsules, known and frequently used in the art, that only disintegrate in the highly acidic environment of the stomach. Also, the vaccine could be mixed with compounds known in the art for
50 temporarily enhancing the pH of the stomach.

Systemic application is also suitable, e.g. by intramuscular application of the vaccine. If this route is followed, standard procedures known in the art for systemic application are well-suited.

5 Another embodiment of the invention relates to diagnostic tests for the detection of *H. felis* infection. It is known that several *Helicobacter* species such as *H. bizzozeronii*, *H. felis* and *H. salomonis* are capable of infecting both cats and dogs. Of these three, *H. felis* is the species suspected to cause most of the pathology, although it is often
10 outnumbered by *H. bizzozeronii* and *H. salomonis*. Thus, a quick and correct diagnosis of disease, in both cats and dogs, caused by *Helicobacter felis* is important. It has however been very difficult to discriminate between these three species due to the fact that they are so very closely related.
Therefore it is another objective of this invention to provide such diagnostic tools suitable for discriminating *H. felis* from other *Helicobacter* species.

15 On the basis of the novel urease polypeptides and the genes encoding the urease polypeptides, at least three different diagnostic tests, specifically suitable for the discrimination of *H. felis* from other members of the *Helicobacter* family were developed:
20 1) a diagnostic test based upon the presence or absence of DNA encoding the specific UreX and UreY structural subunits
2) a diagnostic test based upon the detection of antibodies against the specific UreX and UreY structural subunits
3) a diagnostic test based upon the detection of antigenic material of the specific UreX and UreY structural subunits

25 A diagnostic test according to 1) is e.g. based upon the reaction of bacterial DNA isolated from the animal to be tested, with specific probes or PCR-primers based upon the sequence of ureX or Y genes. If *H. felis* DNA is present in the animal, this will e.g. specifically bind to ureX or Y specific PCR-primers and will subsequently become
30 amplified in PCR-reaction. The PCR-reaction product can then easily be detected in DNA gel electrophoresis.

The DNA can most easily be isolated from the micro-organisms present in swabs of the upper digestive tract or in the saliva of the animal to be tested. Specific primers can easily be selected from the many regions of the ureX and ureY coding sequences and
35 the non-coding intergenic sequence that differ in sequence from the comparable regions in the ureAB coding sequences. One of the many algorithms suitable for the determination of the level of nucleic acid homology and for comparison of nucleotide sequences in general is known as "Clustal W". It has been described by Thompson et al., in Nucleic Acid Research 22: 4673-4680 (1994). The program can be found at
40 several sites on Internet. An more recent alternative for this program is e.g. Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA.

As follows from figure 1, a large number of possible PCR-primers can be found that are specific for ureX or ureY. An extremely specific pair of PCR-probes is e.g. formed by the
45 5'-located sequence CATGCACTTTTGGAAAAAGA (SEQ ID NO: 16) and the 3'-located sequence TATGGTGGTCTTCTCT (SEQ ID NO: 17). Of course many other sequences that are specific for ureX or Y or the intergenic region are suitable. Standard PCR-textbooks give methods for determining the suitability of the probes for selective PCR-reactions with ureX or ureY. PCR-techniques are extensively described in
50 (Dieffenbach & Drexler; PCR primers, a laboratory manual. ISBN 0-87969-447-5 (1995)).

- Another DNA-based test is based upon growth of bacterial material obtained from the swab, followed by classical DNA purification followed by classical hybridisation with radioactively or colour-labelled ureXY-specific DNA-fragments. Given the very low
- 5 homology between the ureXY-coding regions and the ureAB coding regions of both *H. felis* and other *Helicobacter* species, hybridisation unambiguously indicates the presence or absence of *H. felis*. Both PCR-reactions and hybridisation reactions are well-known in the art and are i.a. described in Maniatis/Sambrook (Sambrook, J. *et al.* Molecular cloning: a laboratory manual. ISBN 0-87969-309-6).
- 10 Selective detection with PCR-primers or with classical hybridisation with ureXY-specific DNA-fragments can be done with fragments that preferably are short, but for practical reasons preferably consist of a stretch of at least 10 contiguous nucleotides of SEQ ID NO: 1. It is clear that for hybridisation experiments a probe needs to be selected that has a higher homology to SEQ ID NO: 1, than to sequences encoding the *Helicobacter* ureA
- 15 or ureB subunit. Such a probe can very easily be selected with the help of the Align Plus for Windows program or the Clustal W program as discussed above. In a comparative hybridisation experiment the DNA to be diagnosed can be tested next to e.g. *H. pylori* DNA. The probe according to the invention, having a higher homology to SEQ ID NO: 1 than to a gene encoding ureAB, would bind better to *H. felis* DNA (if present in the sample) than to DNA of other *Helicobacter* species thus specifically revealing the presence of *H. felis* DNA in the sample to be tested. The sequences SEQ ID NO: 16 or
- 20 17 mentioned above are merely examples of probes very suitable for labelling and subsequent use in the *H. felis*-specific hybridisation assays as described.
- 25 Thus, one embodiment of the invention relates to a diagnostic test for the detection of DNA encoding the specific *Helicobacter* UreX and UreY subunit polypeptides. Such a test comprises a nucleic acid sequence according to the invention or a fragment thereof that is specific for the DNA encoding UreX and UreY or the intergenic region between UreX and UreY. A fragment that is specific for that DNA is a fragment that binds better to
- 30 the DNA encoding UreX and UreY or the intergenic region between UreX and UreY than to the DNA encoding UreA and UreB or the intergenic region between UreA and UreB.
- Methods for the detection of *Helicobacter felis* DNA comprise hybridisation of the DNA to be tested with UreX or Y DNA, or PCR-reaction of the DNA to be tested with UreX or Y
- 35 DNA specific probes.

- A diagnostic test according to 2) for the detection of *Helicobacter felis* antibodies in sera can be e.g. a simple sandwich-ELISA-test in which purified UreX or UreY subunit polypeptides or antigenic fragments thereof according to the invention are coated to the
- 40 wall of the wells of an ELISA-plate. A method for the detection of such antibodies is e.g. Incubation of purified UreX or Y polypeptide with serum from mammals to be tested, followed by e.g. incubation with a labelled antibody against the relevant mammalian antibody. A colour reaction can then reveal the presence or absence of antibodies against *Helicobacter felis* urease XY. Depending on the labelled antibodies used, the
- 45 selectivity of this system can be improved by pre-incubation of the serum to be tested with urease AB followed by spinning down the precipitate, in order to avoid non-XY-specific reactions.
- If antigenic fragments of the UreX or UreY structural subunits according to the invention are used for coating, this pre-incubation step can be skipped.

Another example of a diagnostic test system is e.g. the incubation of a Western blot comprising UreX or UreY polypeptide or an antigenic fragment thereof according to the invention, with serum of mammals to be tested, followed by analysis of the blot.

5 The purified UreX and UreY structural subunits or antigenic fragments thereof according to the invention, suitable for the coating of ELISA plates or for Western blotting can easily be obtained by expression of the ureX and ureY gene as was described by Ferrero for ureA and B (Ferrero et al., Molec. Microbiol. 9, 323-333 (1993)).

10 Also, the invention relates to methods for the detection in serum of antibodies against *Helicobacter felis* antibodies in which the method comprises the incubation of serum with UreX or UreY polypeptide or an antigenic fragment thereof according to the invention.

15 A diagnostic test according to 3) based upon the detection of antigenic material of the specific UreX and UreY structural subunits of *Helicobacter felis* antigens and therefore suitable for the detection of *Helicobacter felis* infection can e.g. also be a standard ELISA test. In one example of such a test the walls of the wells of an ELISA plate are coated with antibodies directed against the specific UreX and UreY structural subunits of *Helicobacter felis*. The antigenic material to be tested can if necessary be pre-incubated with antibodies against UreA and B. This will leave the UreX and Y specific epitopes
20 uncovered and therefore the pre-incubated *Helicobacter* species will bind to the ELISA plate only if it comprises UreX or Y, i.e. if it specifically is *Helicobacter felis*.

The use of monoclonal antibodies specific for UreX or Y and not reacting with UreA or B are the preferred antibodies in such tests, because they make the pre-incubation step superfluous. Such monoclonal antibodies can easily be obtained by immunising inbred
25 mice with immunising fragments of UreX or Y according to the invention, by techniques also known in the art (See below: Kohler and Milstein).

30 The polypeptides or immunogenic fragments thereof according to the invention expressed as characterised above can be used to produce antibodies, which may be polyclonal, monospecific or monoclonal (or derivatives thereof). If polyclonal antibodies are desired, techniques for producing and processing polyclonal sera are well-known in the art (e.g. Mayer and Walter, eds. *Immunochemical Methods in Cell and Molecular Biology*, Academic Press, London, 1987).

35 Monoclonal antibodies, reactive against the polypeptide according to the invention (or variants or fragments thereof) according to the present invention, can be prepared by immunising inbred mice by techniques also known in the art (Kohler and Milstein, *Nature*, 256, 495-497, 1975).

40 Finally, the invention relates to methods for the detection of antigenic material from *Helicobacter felis* in which the method comprises the incubation of serum, tissue or body fluids with antibodies against UreX or UreY polypeptide or an antigenic fragment thereof according to the invention.

Example 1

5 The *ureX* and *ureY* genes of *Helicobacter felis* strain CS1: cloning and expression in *Escherichia coli*.

The *ureX* and *ureY* genes of *H. felis* strain CS1 were cloned as an operon into an *E. coli* T7 expression vector, pET3a, as follows:

10 For proper expression of the UreX and Y proteins in pET3a (Novagen, 601 Science Drive, Madison WI, USA) the genes were cloned as a *NdeI*-*Bam*HI DNA fragment into the *NdeI*-*Bam*HI sites of this vector. The *ureaseXY* operon contains an internal *NdeI* site that was mutated by overlap-extension PCR of 2 PCR fragments. For that purpose two PCR fragments (the 5' and the 3' products) were amplified using chromosomal DNA of *H. felis* CS1 as the template. The 5' PCR product contained the complete *ureX* gene and the first part of the *ureY* gene. The forward primer contained a *NdeI* restriction site and the start codon of *ureX* (GGAGTAACATATGAACTCACA CCCAAAGAGC) (SEQ ID NO: 18), and the reverse primer contains a point mutation (CACACCC ACGACCATGTGAGGGCTTAC) (SEQ ID NO: 19). The second, 3' PCR product consisted of the 3' end of the *ureY* gene. This forward primer is complementary to the reverse primer of the first PCR product and also contained the same point mutation (GTAAGCC CTCACATGGTCGTGGGTGTG) (SEQ ID NO: 20), and the reverse primer contained a *Bam*HI restriction site just downstream of the stopcodon of the *ureY* gene (CGAATT CGGATCCTAGAAGAAAGTGTAGCGCTGG) (SEQ ID NO: 21). The mutation in the complementary primers is made to delete the internal *NdeI* site in *ureY*, it replaces the CATATG (His- Met) by CACATG (His-Met).

25 After amplification of both PCR products, the complete operon was obtained by overlap-extension-PCR with the forward primer of the *ureX* and the reverse primer of the *ureY* using both PCR products as templates. The resulting PCR product was cloned into PCR-bluntII-TOPO (Invitrogen, P.O.Box 2312, 9704 CH Groningen, The Netherlands) and transformed into *E. coli* TOP10F' cells (Invitrogen). Positive clones were isolated and the *ureaseXY* genes were sub-cloned into pET3a with *NdeI*-*Bam*HI. The obtained plasmid was called pUreXY-1 and was transformed into the expression strain HMS174(DE3)/pLysS (Novagen).

35 The *ureX* and *ureY* genes of pUreXY-1 were expressed in HMS174(DE3)/pLysS as follows: an overnight culture was diluted 1/100 into TB Amp¹⁰⁰ Cam²⁵; this culture was incubated for 3 h at 37°C at 200 rpm; the culture was induced by adding 1 mM of IPTG and incubated for another 3 h at 37°C at 200 rpm. The induction was done twice, once in a small scale and once in a large scale.

40 The induced samples were analysed on a SDS-PAGE gel (fig. 2). As can be clearly seen from lane 9, expression of UreX and UreY, when induced provides the two structural subunits as polypeptide bands with a molecular weight of 25 kDa for the UreX subunit and 62 kDa for the UreY subunit.

Legend to the figures

- 5 Figure 1a: Comparison of the nucleic acid sequence encoding UreX and Y, including a short non-coding region bridging the two coding sequences, from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the nucleic acid sequence encoding UreA and B, including a short non-coding region bridging the two coding sequences, from *Helicobacter felis*, *pylori* and *heilmannii*
- 10 Figure 1b: Comparison of the amino acid sequence of UreX from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the amino acid sequence encoding UreA from *Helicobacter felis*, *pylori* and *heilmannii*
- 15 Figure 1c: Comparison of the amino acid sequence of UreY from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the amino acid sequence encoding UreB from *Helicobacter felis*, *pylori* and *heilmannii*
- 20 Figure 2: Polyacrylamide gel of the expression products UreX and UreY
- 25 Lane 7 : Biorad broad range marker
 Lane 8 : Complete cell culture before induction (small scale culture)
 Lane 9 : Complete cell culture after induction (small scale culture)
 Lane 10 : Complete cell culture after induction (large scale culture)
 Lane 11 : Supernatant after induction (large scale culture).
 Lane 12 : Biorad pre-stained marker

against ureaseXY.

- 12) Polypeptide according to claims 8-11 for use in a vaccine
- 13) Polypeptide according to claims 8-11 for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.
- 14) Vaccine for combating *Helicobacter felis* infections, characterised in that it comprises a nucleic acid sequence according to claims 1-3, a DNA fragment according to claim 4, a recombinant DNA molecule according to claim 5, a live recombinant carrier according to claim 6, a host cell according to claim 7 or a polypeptide according to claims 8-11, and a pharmaceutically acceptable carrier.
- 15) Vaccine according to claim 14, characterised in that it comprises an adjuvant.
- 16) Vaccine according to claim 14 or 15, characterised in that it comprises an additional antigen derived from a virus or micro-organism pathogenic to mammals or genetic information encoding said antigen.
- 17) Vaccine according to claim 16, characterised in that said virus or micro-organism pathogenic to mammals is selected from the group of Feline Infectious Peritonitis virus, Feline Immune deficiency virus, Canine and Feline Parvovirus, Distemper virus, Adenovirus, Calicivirus, *Bordetella bronchiseptica*, *Borrelia burgdorferi*, *Leptospira interrogans*, *Chlamydia* and *Bartonella henseli*.
- 18) Vaccine for combating *Helicobacter felis* infections, characterised in that it comprises antibodies against a polypeptide according to claims 8-11.
- 19) Method for the preparation of a vaccine according to claims 14-17, said method comprising the admixing of a polypeptide according to claims 8-11 and a pharmaceutically acceptable carrier.
- 20) Diagnostic test for the detection of *Helicobacter felis* specific DNA characterised in that the test comprises a nucleic acid sequence according to claims 1-3, or a fragment thereof.
- 21) Diagnostic test for the detection of antibodies against *Helicobacter felis*, characterised in that said test comprises a polypeptide or a fragment thereof as described in claims 8-11.
- 22) Diagnostic test for the detection of antigenic material of *Helicobacter felis*, characterised in that said test comprises antibodies against a polypeptide or a fragment thereof as described in claims 8-11.

EPO - DG 1

17. 07. 2000

Claims:

- 1) Nucleic acid sequence encoding two subunit polypeptides of a urease complex such as expressed by *Helicobacter felis*, said nucleic acid sequence having at least 85 % homology with SEQ ID NO: 1, or a part thereof encoding at least an immunogenic fragment of one of said subunits, said part having a length of at least 40, preferably 45, more preferably 50 nucleotides.
- 2) Nucleic acid sequence according to claim 1, characterised in that it encodes the urease X subunit polypeptide or the urease Y subunit polypeptide.
- 3) Nucleic acid sequence according to claim 1 or 2, characterised in that the sequence has at least 90 %, preferably 94 %, more preferably 97 % homology therewith.
- 4) DNA fragment comprising a nucleic acid sequence according to claims 1-3
- 5) Recombinant DNA molecule comprising a nucleic acid sequence according to claims 1-3 or a DNA fragment according to claim 4, under the control of a functionally linked promoter.
- 6) Live recombinant carrier comprising a recombinant DNA molecule according to claim 5
- 7) Host cell comprising a nucleic acid sequence according to claims 1-3, a DNA fragment according to claim 4, a recombinant DNA molecule according to claim 5 or a live recombinant carrier according to claim 6.
- 8) *Helicobacter felis* urease X subunit polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or an immunogenic fragment of said polypeptide with a length of at least 40, preferably 45, more preferably 50 amino acids said immunogenic fragment being capable of inducing an immune response against ureaseXY.
- 9) Polypeptide according to claim 8, having a sequence homology of at least 85 %, preferably 90 %, more preferably 95 % homology to SEQ ID NO: 2, or an immunogenic fragment of said polypeptide capable of inducing an immune response against ureaseXY.
- 10) *Helicobacter felis* urease Y subunit polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or an immunogenic fragment of said polypeptide with a length of at least 40, preferably 45, more preferably 50 amino acids said immunogenic fragment being capable of inducing an immune response against ureaseXY.
- 11) Polypeptide according to claim 10, having a sequence homology of at least 85 %, preferably 90 %, more preferably 95 % homology to SEQ ID NO: 3, or an immunogenic fragment of said polypeptide capable of inducing an immune response

17. 07. 2000

Abstract

The present invention relates to novel *Helicobacter felis* urease subunit polypeptides and to nucleic acid sequences encoding these subunit polypeptides, to DNA fragments and recombinant DNA molecules comprising the nucleic acid sequences encoding these subunit polypeptides, to live recombinant carriers and to host cells comprising nucleic acid sequences encoding these subunit polypeptides. Also, the invention relates to the subunit polypeptides for use in vaccines and for use in the manufacturing thereof, to vaccines comprising said subunit polypeptides and to methods for the preparation of such vaccines. Furthermore, the invention relates to diagnostic methods for the detection of *Helicobacter felis* specific nucleic acid sequences, *Helicobacter felis* antigenic material and to antibodies against *Helicobacter felis*.

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ALIGNED SEQUENCES

Reference molecule:	Cslseq	206 -	2603	(2398 bps)	Homology
Sequence 2:	Kukkaseq	48 -	2445	(2398 bps)	94%
Sequence 3:	Ds4seq	2 -	2399	(2398 bps)	94%
Sequence 4:	2301SEQ	1 -	2398	(2398 bps)	94%
Sequence 5:	390seq	3 -	2181	(2179 bps)	85%
Sequence 6:	H. felis comp	43 -	2475	(2433 bps)	67%
Sequence 7:	H. pylori com	2659 -	5088	(2430 bps)	67%
Sequence 8:	H. heilmannii	211 -	2636	(2426 bps)	68%

Alignment type: Global DNA
Parameters: Mismatch 1;

GLOBAL DNA
Mismatch 1: Open Gap 3: Extend Gap 3

[illegible]

Figure 1a (1)

Figure 1a (2)

```

ureyCS1
ureykuka
ureyDS4
urey2301
urey390
B felis
B pylori
B heilman

( 480) hhgkakfdtsitfvskvayengvkekglglervqvpvkncrnitkkdkfndktakitvdokttfevfdgklctskptsqvpqlaqrytff
( 480) .....k.....e.....
( 480) .....k.....a.e.....
( 480) .....k.....n..h.....a.e.....
( 480) .....k.....n..h.....a.e.....rvss
( 480) .....n.....i...v..h.d.n.e.yk.k...ev...aadeis...l.nl.
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Figure 1c (2)

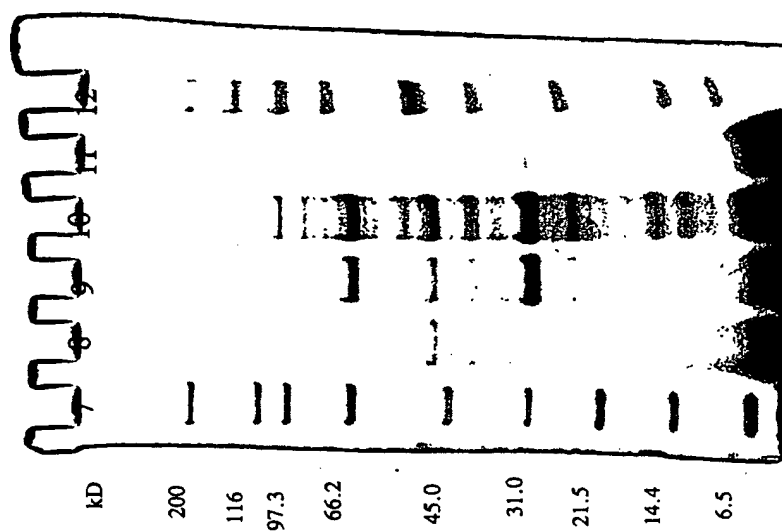


Figure 2

SEQUENCE LISTING

EPO-DG 1

17. 07. 2000

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<141>

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<220>

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<220>

<221> CDS

<222> (692)..(2398)

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1					5					10					15	

ggc	gaa	gtg	gct	aga	aag	cgc	aaa	gca	gag	ggc	tta	aag	ctc	aat	caa	96
Gly	Glu	Val	Ala	Arg	Lys	Arg	Lys	Ala	Glu	Gly	Leu	Lys	Leu	Asn	Gln	
			20					25					30			

ccc	gaa	gcc	att	gcc	tac	att	agt	gcc	cat	att	atg	gac	gag	gcg	cgc	144
Pro	Glu	Ala	Ile	Ala	Tyr	Ile	Ser	Ala	His	Ile	Met	Asp	Glu	Ala	Arg	
		35					40					45				

cgt	ggc	aaa	aaa	acc	gtt	gct	gaa	ctt	atg	gaa	gaa	tgt	atg	cac	ttt	192
Arg	Gly	Lys	Lys	Thr	Val	Ala	Glu	Leu	Met	Glu	Glu	Cys	Met	His	Phe	
	50					55					60					

ttg	aaa	aaa	gat	gag	gtg	atg	ccc	ggg	gtg	ggg	aat	atg	gtc	cct	gat	240
Leu	Lys	Lys	Asp	Glu	Val	Met	Pro	Gly	Val	Gly	Asn	Met	Val	Pro	Asp	
65					70					75					80	

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Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                        85                      90                      95

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Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
                        100                     105                     110

ttt ggc tgt gat aaa gac att gag ctc aac gcg ggt aag gaa gtt acc      384
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
                        115                     120                     125

gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc      432
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
                        130                     135                     140

cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg gaa      480
His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
                        145                     150                     155                     160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc      528
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                        165                     170                     175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt      576
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
                        180                     185                     190

agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac      624
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
                        195                     200                     205

gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga ttc      672
Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
                        210                     215                     220

atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aac      721
Ile Lys                      Met Lys Met Lys Lys Gln Glu Tyr Val Asn
                        225                     230                     235

acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat      769
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
                        240                     245                     250

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Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
                        255                     260                     265

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agc cca gat gaa aac acc tta gat tta	gtg atc acc aac gcg atg att	913	
Ser Pro Asp Glu Asn Thr Leu Asp Leu	Val Ile Thr Asn Ala Met Ile		
290	295 300		
atc gac tac acc ggg att tat aaa gcc	gac att ggt att aaa aat ggc	961	
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala	Asp Ile Gly Ile Lys Asn Gly		
305	310 315		
aaa atc cat ggt att ggc aag gcg ggg	aac aaa gac atg caa gat ggc	1009	
Lys Ile His Gly Ile Gly Lys Ala Gly	Asn Lys Asp Met Gln Asp Gly		
320	325 330		
gta agc cct cat atg gtc gtg ggt gtg	ggc aca gaa gca cta gca ggg	1057	
Val Ser Pro His Met Val Val Gly Val	Gly Thr Glu Ala Leu Ala Gly		
335	340 345		
gaa ggt atg att att acc gct ggg ggg	atc gat tcg cac acc cac ttc	1105	
Glu Gly Met Ile Ile Thr Ala Gly Gly	Ile Asp Ser His Thr His Phe		
350	355 360 365		
ctc tct ccc caa caa ttc cct acc gct	cta gcc aat ggt gtt aca acc	1153	
Leu Ser Pro Gln Gln Phe Pro Thr Ala	Leu Ala Asn Gly Val Thr Thr		
370	375 380		
atg ttt gga ggt ggc aca ggt ccg gta	gat ggc acg aat gcg acc acc	1201	
Met Phe Gly Gly Gly Thr Gly Pro Val	Asp Gly Thr Asn Ala Thr Thr		
385	390 395		
atc act ccg ggc aaa tgg aac ttg cac	cgc atg ttg cgc gca gct gaa	1249	
Ile Thr Pro Gly Lys Trp Asn Leu His	Arg Met Leu Arg Ala Ala Glu		
400	405 410		
gag tat tct atg aat gtg ggc ttt ttg	ggc aaa ggc aat agc tcc agt	1297	
Glu Tyr Ser Met Asn Val Gly Phe Leu	Gly Lys Gly Asn Ser Ser Ser		
415	420 425		
aaa aaa caa ctc gta gaa caa gta gaa	gcg ggc gcg att ggc ttt aaa	1345	
Lys Lys Gln Leu Val Glu Gln Val Glu	Ala Gly Ala Ile Gly Phe Lys		
430	435 440 445		
ttg cat gaa gac tgg ggc aca aca cca	agt gcg atc gat cac tgc ttg	1393	
Leu His Glu Asp Trp Gly Thr Thr Pro	Ser Ala Ile Asp His Cys Leu		
450	455 460		

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agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg 1441
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
      465              470              475

gtc aat gag gca ggt tat gta gat gac acc cta aat gcg atg aac ggg 1489
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
      480              485              490

cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca 1537
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
      495              500              505

cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc 1585
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
      510              515              520              525

acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac tta 1633
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
      530              535              540

gac atg ctc atg acc tgc cac cac cta gac aaa cgc atc cgc gag gat 1681
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
      545              550              555

ctc cag ttt tcc caa agc cgt atc cgc ccc ggc tct att gcc gct gaa 1729
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
      560              565              570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg 1777
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
      575              580              585

caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa act 1825
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
      590              595              600              605

gca gac aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca 1873
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala
      610              615              620

gat aat gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att 1921
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
      625              630              635

aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa 1969
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
      640              645              650

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gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gct ttc ttt ggt 2017
 Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
 655 660 665

gta aaa ccc aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa 2065
 Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
 670 675 680 685

atg ggc gat tct aac gcg tct gtg ccc aca cct cag ccg gtt tat tac 2113
 Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
 690 695 700

cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc 2161
 Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
 705 710 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta 2209
 Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
 720 725 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act 2257
 Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
 735 740 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat 2305
 Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
 750 755 760 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa 2353
 Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
 770 775 780

ccc gcc tct gaa gtg cct cta gcc caa cgc tac act ttc ttc tag 2398
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gcacaat 2405

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<213> Helicobacter felis

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Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
 20 25 30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
 35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
 50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
 85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
 100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
 115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
 130 135 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
 145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
 165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
 180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
 195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
 210 215 220

Ile Lys
 225

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 20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
 35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
 50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
 85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
 100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
 115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
 130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
 145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
 165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
 180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
 195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
 210 215 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
 225 230 235 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr

245	250	255
Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr		
260	265	270
His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met		
275	280	285
Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro		
290	295	300
Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys		
305	310	315 320
His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser		
325	330	335
Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile		
340	345	350
Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala		
355	360	365
Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys		
370	375	380
Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg		
385	390	395 400
Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His		
405	410	415
Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp		
420	425	430
Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val		
435	440	445
Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala		
450	455	460
Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His		
465	470	475 480
His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val		
485	490	495
Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val		

500 505 510
 Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
 515 520 525
 Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
 530 535 540
 Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
 545 550 555 560
 Leu Ala Gln Arg Tyr Thr Phe Phe
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 gcg ggc gaa gtg gct aga aag cgc aaa gca gag ggc tta aag ctc aat 95
 Ala Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn
 20 25 30
 caa ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg 143
 Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala
 35 40 45
 cgc cgt ggc aaa aaa acc gtt gct gaa ctt atg gaa gaa tgt atg cac 191
 Arg Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His
 50 55 60
 ttt ttg aaa aaa gat gag gtg atg ccc ggt gtg ggg aat atg gtc cct 239
 Phe Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro

65	70	75	
gat ttg ggc gta gaa gcc act ttc ccc gat ggc acc aaa ctc gta acc			287
Asp Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr			
80	85	90	95
gtg aat tgg ccc att gaa cct gat gaa cac ttt aaa gcc ggt gaa gtg			335
Val Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val			
100	105	110	
aaa ttt ggc tgt gat aaa gac att gag ctc aac gtg ggt aag gaa gtt			383
Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val			
115	120	125	
acc gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt			431
Thr Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly			
130	135	140	
agc cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg			479
Ser His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg			
145	150	155	
gaa aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta			527
Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu			
160	165	170	175
cgc att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc			575
Arg Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly			
180	185	190	
ggg agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg			623
Gly Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala			
195	200	205	
gac gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga			671
Asp Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly			
210	215	220	
ttc atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta			720
Phe Ile Lys Met Lys Met Lys Lys Gln Glu Tyr Val			
225	230	235	
aac acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc			768
Asn Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr			
240	245	250	
gat ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag			816
Asp Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu			

255	260	265	
ctc aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc			864
Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser			
270	275	280	
aat agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg			912
Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met			
285	290	295	300
att atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat			960
Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn			
305	310	315	
ggc aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat			1008
Gly Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp			
320	325	330	
ggc gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca			1056
Gly Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala			
335	340	345	
ggg gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac			1104
Gly Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His			
350	355	360	
ttc ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca			1152
Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr			
365	370	375	380
acc atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc			1200
Thr Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr			
385	390	395	
acc atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct			1248
Thr Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala			
400	405	410	
gaa gag tat tct atg aat gta ggc ttt ttg ggc aaa ggc aat agt tct			1296
Glu Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser			
415	420	425	
agc aaa aaa caa ctt gta gaa caa gta gaa gcg ggc gcg att ggc ttt			1344
Ser Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe			
430	435	440	
aaa ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc			1392
Lys Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys			

445	450	455	460
ttg agc gtg gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat			1440
Leu Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp			
465	470	475	
acg gtc aat gag gca ggt tat gtg gat gac acc cta aat gca atg aac			1488
Thr Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn			
480	485	490	
ggg cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac			1536
Gly Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His			
495	500	505	
tca cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc			1584
Ser Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser			
510	515	520	
tcc acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac			1632
Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His			
525	530	535	540
tta gac atg ctc atg acc tgc cac cac cta gat aag cgc atc cgc gag			1680
Leu Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu			
545	550	555	
gat tta caa ttt tct caa agc cgt atc cgc ccc gga tct att gcc gct			1728
Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala			
560	565	570	
gag gat gtg ctc cat gat att ggc gtg atc gcg atg act agc tcc gat			1776
Glu Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp			
575	580	585	
tcg caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa			1824
Ser Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln			
590	595	600	
act gca gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt			1872
Thr Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly			
605	610	615	620
gca gat aac gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc			1920
Ala Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr			
625	630	635	
att aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg			1968
Ile Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val			

640	645	650	
gaa gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt			2016
Glu Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe			
655	660	665	
ggc gtg aaa cct aag att gtg att aaa ggt ggc atg gtg gtc ttc tct			2064
Gly Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser			
670	675	680	
gaa atg ggc gat tct aac gcg tcc gtg ccc acg cct cag ccg gtt tat			2112
Glu Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr			
685	690	695	700
tac cgc gaa atg ttt ggg cac cac ggc aag gcg aaa ttt gac acc agc			2160
Tyr Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser			
705	710	715	
atc act ttt cgt gtc tca agc gg			2183
Ile Thr Phe Arg Val Ser Ser			
720			
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Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg			
35	40	45	
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe			
50	55	60	
Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp			
65	70	75	80
Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val			
85	90	95	
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys			

100 105 110
 Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val Thr
 115 120 125
 Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
 130 135 140
 His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
 145 150 155 160
 Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
 165 170 175
 Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
 180 185 190
 Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
 195 200 205
 Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
 210 215 220
 Ile Lys
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 His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
 35 40 45
 Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
 50 55 60
 Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225 230 235 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
245 250 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
260 265 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
 340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
 355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
 370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
 385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
 405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
 420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
 435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
 450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
 465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Arg Val Ser Ser
 485 490 495

<210> 7

<211> 2883

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<213> Helicobacter felis

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<222> (206)..(886)

<220>

<221> CDS

<222> (897)..(2603)

<400> 7

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ttacttatat taaaaagtta ataaaaagta acgaaattag gactataatc ccattgcctt 180

taaaatttaa cacaaggagt aatag gtg aaa ctc aca ccc aaa gag caa gaa 232
Val Lys Leu Thr Pro Lys Glu Gln Glu
1 5

aag ttc ttg tta tat tat gcg ggc gaa gtg gct aga aag cgc aaa gca 280
Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val Ala Arg Lys Arg Lys Ala
10 15 20 25

gag ggc tta aag ctc aac caa ccc gaa gcc att gct tac att agt gcc 328
Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala
30 35 40

cat att atg gac gaa gcg cgc cgt gga aaa aaa acc gtt gcc cag ctt 376
His Ile Met Asp Glu Ala Arg Arg Gly Lys Lys Thr Val Ala Gln Leu
45 50 55

atg gaa gag tgc atg cac ttt ttg aaa aaa gat gaa gta atg ccc ggg 424
Met Glu Glu Cys Met His Phe Leu Lys Lys Asp Glu Val Met Pro Gly
60 65 70

gtg ggt aat atg gtt ccc gat cta ggt gta gaa gcc acc ttt cct gat 472
Val Gly Asn Met Val Pro Asp Leu Gly Val Glu Ala Thr Phe Pro Asp
75 80 85

ggt acg aaa ctt gta act gtg aat tgg ccc atc gaa cca gat gag cac 520
Gly Thr Lys Leu Val Thr Val Asn Trp Pro Ile Glu Pro Asp Glu His
90 95 100 105

ttc aaa gcg ggc gaa gtg aaa ttt ggt tgc gat aaa gac atc gag ctc 568
Phe Lys Ala Gly Glu Val Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu
110 115 120

aat gca ggc aaa gaa gta acc gaa ctt gag gtt act aat gaa ggg cct 616
Asn Ala Gly Lys Glu Val Thr Glu Leu Glu Val Thr Asn Glu Gly Pro
125 130 135

aaa tcc ttg cat gtg ggt agc cat ttc cac ttc ttt gaa gct aac aag 664
Lys Ser Leu His Val Gly Ser His Phe His Phe Phe Glu Ala Asn Lys
140 145 150

gca cta aaa ttc gat cgt gaa aaa gcc tat ggc aaa cgc cta gat att 712
Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile
155 160 165

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ccc tct ggc aac acg cta cgc att ggg gca gga caa acc cgc aaa gtg      760
Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala Gly Gln Thr Arg Lys Val
170                      175                      180                      185

cag ttg att cct ctt ggt ggc agt aaa aaa gtg att ggc atg aac ggg      808
Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys Val Ile Gly Met Asn Gly
                      190                      195                      200

ctt gtg aat aac atc gcg gat gaa cgc cat aaa cat aaa gcg ctt gac      856
Leu Val Asn Asn Ile Ala Asp Glu Arg His Lys His Lys Ala Leu Asp
                      205                      210                      215

aag gcg aaa tct cac gga ttt atc aag taa ggagactccc atg aaa atg      905
Lys Ala Lys Ser His Gly Phe Ile Lys                      Met Lys Met
                      220                      225                      230

aaa aaa caa gaa tat gta aat acc tac gga ccc acc aaa ggc gat aaa      953
Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Lys Gly Asp Lys
                      235                      240                      245

gtg cgc tta gga gat acc gat ctt tgg gca gaa gta gaa cat gac tat      1001
Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu His Asp Tyr
                      250                      255                      260

acc acc tat ggc gaa gaa ctt aaa ttt ggc gcg ggt aaa act atc cgt      1049
Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg
                      265                      270                      275

gag ggt atg ggt cag agc aat agc cct gat gaa aac acc cta gat tta      1097
Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu
                      280                      285                      290

gtc atc act aac gcg atg att atc gac tac acc ggg att tac aaa gcc      1145
Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala
295                      300                      305                      310

gac att ggg att aaa aac ggc aaa atc cat ggc att ggc aag gca gga      1193
Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly Lys Ala Gly
                      315                      320                      325

aac aag gac atg caa gat ggc gta agc cct cat atg gtc gtg ggt gtg      1241
Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val Val Gly Val
                      330                      335                      340

ggc aca gaa gca cta gca ggg gaa ggt atg att att acc gct ggg gga      1289
Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr Ala Gly Gly
                      345                      350                      355

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atc gat tca cac acc cac ttc ctt tct cca caa caa ttc cct acc gct 1337
 Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala
 360 365 370

cta gcc aat ggc gtt aca acc atg ttt gga ggc ggc aca ggt cct gta 1385
 Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr Gly Pro Val
 375 380 385 390

gat ggc acg aat gcg act act atc act ccg ggc aaa tgg aac ttg cac 1433
 Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp Asn Leu His
 395 400 405

cgc atg ttg cgc gca gca gaa gag tat tct atg aat gtg ggc ttt ttg 1481
 Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val Gly Phe Leu
 410 415 420

ggc aaa ggc aat agc tct agc aaa aaa caa ctt gta gaa caa gta gaa 1529
 Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu Gln Val Glu
 425 430 435

gcg ggc gcg att ggt ttt aaa ttg cat gaa gac tgg ggc aca aca cca 1577
 Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly Thr Thr Pro
 440 445 450

agt gcg atc gat cac tgc ttg agc gtg gca gat gaa tac gat gtg caa 1625
 Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr Asp Val Gln
 455 460 465 470

gtt tgt atc cac acc gat aca gtc aat gag gca ggt tat gta gat gac 1673
 Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr Val Asp Asp
 475 480 485

acc cta aat gca atg aac ggg cgc gcc atc cat gcc tac cac att gag 1721
 Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr His Ile Glu
 490 495 500

gga gcg ggt gga gga cac tca cct gat gtt atc acc atg gca ggc gag 1769
 Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met Ala Gly Glu
 505 510 515

ctc aat att cta ccc tcc tcc acc acc ccc act att ccc tat acc att 1817
 Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile
 520 525 530

aat acg gtt gca gaa cac tta gac atg ctc atg aca tgc cac cac cta 1865
 Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys His His Leu
 535 540 545 550

gac aaa cgc atc cgc gag gat tta caa ttt tct caa agc cgt atc cgc	1913
Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg	
555 560 565	
ccc ggc tct atc gcg gct gaa gat gtg ctc cat gat atg ggt gtg atc	1961
Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Met Gly Val Ile	
570 575 580	
gcg atg aca agc tcg gat tcg caa gca atg ggg cgt gca ggc gaa gtg	2009
Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala Gly Glu Val	
585 590 595	
att cct cga act tgg cag act gcg gat aag aat aaa aaa gaa ttt ggt	2057
Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys Glu Phe Gly	
600 605 610	
aag ctt cct gaa gat ggc aaa gat aac gat aat ttc cgc att aag cgc	2105
Lys Leu Pro Glu Asp Gly Lys Asp Asn Asp Asn Phe Arg Ile Lys Arg	
615 620 625 630	
tac atc tcc aaa tac act atc aac ccc gct ttg acc cac ggc gtg agc	2153
Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His Gly Val Ser	
635 640 645	
gag tat atc ggc tct gtg gaa gag ggc aag atc gcc gac ttg gtg gtg	2201
Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp Leu Val Val	
650 655 660	
tgg aat cct gcc ttt ttt ggc gta aaa ccc aaa atc gtg atc aaa ggc	2249
Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val Ile Lys Gly	
665 670 675	
ggg atg gtg gtc ttc tct gaa atg ggc gat tct aac gcg tct gtg ccc	2297
Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala Ser Val Pro	
680 685 690	
act ccc caa ccg gtt tat tac cgc gaa atg ttt ggg cat cac ggc aag	2345
Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His His Gly Lys	
695 700 705 710	
gcg aaa ttt gac acc agc atc act ttt gtt tcc aaa gtc gcc tat gaa	2393
Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val Ala Tyr Glu	
715 720 725	
aat ggc gtg aaa gaa aag ctg ggc tta gag cgc caa gtt cta ccg gtc	2441
Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Gln Val Leu Pro Val	
730 735 740	

aaa aac tgc cgt aac atc acc aag aaa gac ttc aag ttc aac gac aaa 2489
 Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe Asn Asp Lys
 745 750 755

acg gca aaa atc acc gtc gat ccg aaa acc ttc gag gtc ttt gta gat 2537
 Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val Phe Val Asp
 760 765 770

ggc aaa ctc tgc acc tct aaa ccc acc tcg caa gtg cct cta gcc cag 2585
 Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Gln Val Pro Leu Ala Gln
 775 780 785 790

cgc tac act ttc ttc tag gcacaatgcc ccctttgggg gcagggttatt 2633
 Arg Tyr Thr Phe Phe
 795

ttaggaatct tcataaaacg cacctgcaat cggctcttgcg tgtgcgatcg tgtcgcttta 2693

aaacaacttt tcacttttaa gcaatcgcca tttttaatta atttaattct tataattaat 2753

attatattat gccccctcat ttttaaagga gaattatgcg taggtctttg gtattgctat 2813

gtggggggttg tttggtgctg ggcgcaaagg gtattgaaac ccatcgctc aaaaaagtag 2873

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<213> Helicobacter felis

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 20 25 30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
 35 40 45

Arg Gly Lys Lys Thr Val Ala Gln Leu Met Glu Glu Cys Met His Phe
 50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

<210> 9

<211> 568

<212> PRT

<213> Helicobacter felis

<400> 9

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Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65 70 75 80
 Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
 85 90 95
 Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
 100 105 110
 Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
 115 120 125
 Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
 130 135 140
 Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
 145 150 155 160
 Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
 165 170 175
 Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
 180 185 190
 Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
 195 200 205
 Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
 210 215 220
 Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
 225 230 235 240
 Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
 245 250 255
 Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
 260 265 270
 His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
 275 280 285
 Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
 290 295 300
 Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
 305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
 325 330 335
 Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Met
 340 345 350
 Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
 355 360 365
 Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
 370 375 380
 Glu Phe Gly Lys Leu Pro Glu Asp Gly Lys Asp Asn Asp Asn Phe Arg
 385 390 395 400
 Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
 405 410 415
 Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
 420 425 430
 Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
 435 440 445
 Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
 450 455 460
 Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
 465 470 475 480
 His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
 485 490 495
 Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Gln Val
 500 505 510
 Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
 515 520 525
 Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val
 530 535 540
 Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Gln Val Pro
 545 550 555 560
 Leu Ala Gln Arg Tyr Thr Phe Phe
 565

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 Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
 1 5 10 15

ggc gaa gtg gct aga aag cgc aaa gcg gag ggc tta aag ctc aac caa 97
 Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
 20 25 30

ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg cgc 145
 Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
 35 40 45

cgt ggc aaa aag acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt 193
 Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
 50 55 60

ttg aaa aaa gac gag gtg atg ccc ggt gtg ggg aat atg gtc cct gat 241
 Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65 70 75 80

tta ggc gtg gaa gct act ttt ccc gat ggc acc aaa ctc gta acc gtg 289
 Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
 85 90 95

aat tgg ccc atc gaa ccc gat gaa cac ttc aaa gcg ggc gaa gtc aaa 337
 Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
 100 105 110

ttt ggc tgt gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc 385
 Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
 115 120 125

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gaa cta gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc 433
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

cat ttc cac ttc ttt gaa gcc aac aag gca ttg aaa ttc gat cgg gaa 481
His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc 529
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggc 577
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gca gat 625
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

gaa cgc cat aaa cac aaa gcg tta gaa aaa gca aaa tct cac gga ttt 673
Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
210 215 220

atc aaa taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aat 722
Ile Lys Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225 230 235

acc tac gga cct acc aca ggc gac aaa gtg cgc tta gga gat acc gat 770
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
240 245 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc 818
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
255 260 265

aaa ttt ggc gcg ggt aaa act atc cgt gag ggc atg ggt cag agc aat 866
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270 275 280 285

agt cca gat gaa aac acc cta gat tta gtc atc acc aac gcg atg att 914
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
290 295 300

att gac tac acc ggg att tac aaa gcc gac att ggc att aaa aat ggc 962
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
305 310 315

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aaa atc cat ggc att ggc aag gca gga aac aag gac atg caa gat ggc 1010
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
      320              325              330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca tta gca ggg 1058
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
      335              340              345

gaa ggt atg att att acc gct ggg ggg atc gat tca cac acc cac ttc 1106
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
      350              355              360              365

ctc tct cca caa caa ttc cct acc gct cta gcc aat ggc gtt aca acc 1154
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
      370              375              380

atg ttt ggc ggt ggc aca ggt ccg gta gat ggc acg aat gcg act acc 1202
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
      385              390              395

atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa 1250
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
      400              405              410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt 1298
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
      415              420              425

aaa aaa caa ctt gta gaa caa ata gaa gcg ggc gcg atc ggc ttt aaa 1346
Lys Lys Gln Leu Val Glu Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys
      430              435              440              445

ttg cat gaa gac tgg ggc aca act cca agt gca atc gat cac tgc ttg 1394
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
      450              455              460

agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg 1442
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
      465              470              475

gtc aat gag gca ggt tat gta gat gac acc ctg aat gcg atg aac ggg 1490
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
      480              485              490

cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca 1538
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
      495              500              505

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cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc 1586
 Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
 510 515 520 525

aca acc ccc act atc ccc tat acc att aat acg gtt gca gaa cac tta 1634
 Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
 530 535 540

gac atg ctc atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat 1682
 Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
 545 550 555

tta caa ttt tcc caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa 1730
 Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
 560 565 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg 1778
 Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
 575 580 585

caa gca atg ggg cgc gct ggc gaa gtg att cct cga act tgg cag act 1826
 Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
 590 595 600 605

gcg gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat agt gca 1874
 Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala
 610 615 620

gat aac gac aac ttc cgt atc aaa cgc tac atc tcc aaa tac act att 1922
 Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
 625 630 635

aac ccc gct cta acc cat ggg gta agc gag tat atc ggc tct gtg gaa 1970
 Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
 640 645 650

gag ggc aaa atc gct gat ttg gtg gtg tgg aat cct gcc ttt ttt ggt 2018
 Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
 655 660 665

gtg aaa cct aag att gtg atc aaa ggc ggt atg gtg gtc ttc tct gaa 2066
 Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
 670 675 680 685

atg ggc gac tcc aac gcg tcc gtg cct aca cct cag ccg gtt tat tac 2114
 Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
 690 695 700

cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc 2162
 Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
 705 710 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta 2210
 Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
 720 725 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act 2258
 Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
 735 740 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat 2306
 Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
 750 755 760 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa 2354
 Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
 770 775 780

ccc gcc tct gaa gtg cct cta gcc cag cgc tac act ttc ttc tag 2399
 Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
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gcncaatg 2407

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<211> 226

<212> PRT

<213> Helicobacter felis

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
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Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
 20 25 30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
 35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
 50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

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<211> 568

<212> PRT

<213> Helicobacter felis

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20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr

50	55	60
Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile		
65	70	75 80
Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly		
	85	90 95
Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val		
	100	105 110
Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr		
	115	120 125
Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe		
	130	135 140
Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr		
	145	150 155 160
Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp		
	165	170 175
Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val		
	180	185 190
Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu		
	195	200 205
Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly		
	210	215 220
Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr		
	225	230 235 240
Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr		
	245	250 255
Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr		
	260	265 270
His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met		
	275	280 285
Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro		
	290	295 300
Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys		

305 310 315 320
 His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
 325 330 335
 Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
 340 345 350
 Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
 355 360 365
 Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
 370 375 380
 Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala Asp Asn Asp Asn Phe Arg
 385 390 395 400
 Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
 405 410 415
 Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
 420 425 430
 Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
 435 440 445
 Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
 450 455 460
 Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
 465 470 475 480
 His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
 485 490 495
 Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
 500 505 510
 Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
 515 520 525
 Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
 530 535 540
 Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
 545 550 555 560
 Leu Ala Gln Arg Tyr Thr Phe Phe

565

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 Val Lys Leu
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aca ccc aaa gag caa gaa aag ttc ttg tta tat tat gcg ggc gaa gtg 104
 Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val
 5 10 15

gct aga aag cgc aaa gca gag ggc tta aag ctc aac caa ccc gaa gcc 152
 Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala
 20 25 30 35

att gcc tac att agt gcc cat att atg gac gag gcg cgt cgt ggc aaa 200
 Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg Arg Gly Lys
 40 45 50

aaa acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt ttg aaa aaa 248
 Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe Leu Lys Lys
 55 60 65

gac gag gtg atg ccc ggg gtg ggg aat atg gtc cct gat ttg ggc gtg 296
 Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp Leu Gly Val
 70 75 80

gaa gcc act ttc ccc gat ggc acc aaa ctc gta act gtg aat tgg ccc 344
 Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val Asn Trp Pro
 85 90 95

atc gaa cct gat gaa cac ttt aag gcg ggt gaa gtg aaa ttt ggc tgt 392
 Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys Phe Gly Cys

100	105	110	115	
gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc gaa cta gaa				440
Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr Glu Leu Glu				
120	125	130		
gtt act aac gaa gga cct aaa tcc ttg cat gtg ggt agc cat ttc cac				488
Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser His Phe His				
135	140	145		
ttc ttt gaa gcc aac aaa gca ttg aaa ttc gat cgg gaa aaa gcc tat				536
Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr				
150	155	160		
ggc aaa cgc cta gat att ccc tct ggc aac aca cta cgc att ggg gca				584
Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala				
165	170	175		
gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt agt aaa aaa				632
Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys				
180	185	190	195	
gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac gaa cgc cat				680
Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp Glu Arg His				
200	205	210		
aaa cac aaa gcg cta gac aaa gca aaa tct cac gga ttt atc aag taa				728
Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe Ile Lys				
215	220	225		
ggagactccc atg aaa atg aaa aaa caa gag tat gta aat acc tac gga				777
Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly				
230	235	240		
ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat ctt tgg gca				825
Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala				
245	250	255		
gaa gta gaa cat gac tat acc acc tat ggc gaa gaa ctc aaa ttc ggt				873
Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly				
260	265	270		
gca ggt aaa act atc cgt gag ggt atg ggt cag agc aat agc cca gat				921
Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp				
275	280	285		
gaa aac acc tta gat tta gtg atc acc aac gcg atg att att gac tac				969
Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr				

290	295	300	
acc ggg att tac aaa gcc gac att ggc att aaa aat ggc aaa atc cat			1017
Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His			
305	310	315	320
ggc att ggc aag gca gga aac aag gac atg caa gat ggc gta agc cct			1065
Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro			
	325	330	335
cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg gaa ggt atg			1113
His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met			
	340	345	350
att att acc gct ggg ggg atc gat tca cac acc cac ttc ctc tct cca			1161
Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro			
	355	360	365
caa caa ttc cct acc gct cta gcc aat ggc gtt aca aca atg ttt ggc			1209
Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly			
	370	375	380
ggt ggc aca ggc ccc gta gat ggc acg aat gcg act acc atc act ccg			1257
Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro			
	385	390	400
ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gca gaa gag tat tct			1305
Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser			
	405	410	415
atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tct agt aaa aaa caa			1353
Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln			
	420	425	430
ctt gta gaa caa gta gaa gcg ggc gcg att ggt ttt aaa ttg cat gaa			1401
Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu			
	435	440	445
gac tgg ggc aca act cca agt gcg atc gat cac tgc ttg agc gta gca			1449
Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala			
	450	455	460
gat gaa tac gat gtg caa gtt tgt ata cac acc gat acg gtc aat gag			1497
Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu			
	465	470	480
gca ggt tat gta gat gac acc cta aat gca atg aac ggg cgc gcc atc			1545
Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile			

485	490	495	
cat gcc tac cac att gag gga gcg ggt gga gga cac tca cct gat gtt			1593
His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val			
500	505	510	
atc acc atg gca ggc gaa gtg aat att cta ccc tcc tcc aca acc cct			1641
Ile Thr Met Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro			
515	520	525	
act atc ccc tat acc att aat acg gtt gca gaa cac tta gac atg ctt			1689
Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu			
530	535	540	
atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat ctc caa ttt			1737
Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe			
545	550	555	560
tct caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa gat gtg ctc			1785
Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu			
565	570	575	
cat gat atc ggt gtg atc gcg atg aca agt tcc gat tcg caa gca atg			1833
His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met			
580	585	590	
ggg cgc gct ggg gaa gtg att cct aga act tgg caa act gca gac aag			1881
Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys			
595	600	605	
aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca gat aat gac			1929
Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp			
610	615	620	
aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att aat ccc gct			1977
Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala			
625	630	635	640
ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa gag ggc aag			2025
Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys			
645	650	655	
atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt ggc gta aaa ccc			2073
Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro			
660	665	670	
aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa atg ggc gat			2121
Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp			

675	680	685	
tct aat gcg tct gtg ccc act cct cag ccg gtt tat tac cgc gaa atg			2169
Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met			
690	695	700	
ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc act ttt gtt			2217
Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val			
705	710	715	720
tcc aaa gtc gcc tat gaa aat ggt gtg aaa gaa aaa cta ggt tta gag			2265
Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu			
725	730	735	
cgc aag gtg ctc ccc gtg aaa aac tgc cgt aac atc acc aag aag gac			2313
Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp			
740	745	750	
ttc aag ttc aac gac aaa act gca aaa atc acc gtc gat ccg aaa acc			2361
Phe Lys Phe Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr			
755	760	765	
ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa ccc acc tct			2409
Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser			
770	775	780	
gaa gtg cct cta gcc caa cgc tac act ttc ttc tag gcataat			2452
Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe			
785	790	795	
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Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln			
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Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg			
35	40	45	
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe			
50	55	60	

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

<210> 15

<211> 568

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Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys

35	40	45
Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr		
50	55	60
Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile		
65	70	75 80
Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly		
85	90	95
Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val		
100	105	110
Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr		
115	120	125
Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe		
130	135	140
Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr		
145	150	155 160
Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp		
165	170	175
Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val		
180	185	190
Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu		
195	200	205
Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly		
210	215	220
Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr		
225	230	235 240
Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr		
245	250	255
Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr		
260	265	270
His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met		
275	280	285
Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro		

290	295	300
Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys		
305	310	315 320
His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser		
	325	330 335
Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile		
	340	345 350
Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala		
	355	360 365
Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys		
	370	375 380
Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg		
385	390	395 400
Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His		
	405	410 415
Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp		
	420	425 430
Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val		
	435	440 445
Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala		
450	455	460
Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His		
465	470	475 480
His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val		
	485	490 495
Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val		
	500	505 510
Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe		
	515	520 525
Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val		
530	535	540
Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Glu Val Pro		

545

550

555

560

Leu Ala Gln Arg Tyr Thr Phe Phe
565

